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## The relation between ADHD symptoms and fine motor control: A genetic study

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Previous research has shown that fine motor control (MC) performance, measured with a computerized task, was less accurate in children with ADHD and in their unaffected siblings, compared to healthy children. This might indicate a shared genetic etiology between MC and ADHD; it was therefore suggested that MC could serve as endophenotype for ADHD. We examined the association between ADHD symptoms (AS) and MC in a genetically informative design that can distinguish between a genetic and a nongenetic familial etiology for the association. Participants were 12-year-old twins and their siblings ( $N = 409$ ). AS were rated on a continuous scale with the Strengths and Weaknesses of ADHD and Normal behavior scale (SWAN). MC accuracy and stability was measured with the computerized pursuit task of the Amsterdam Neuropsychological Tasks (ANT). Analyses were performed with Structural Equation Modelling. AS were weakly associated with MC accuracy of the left and right hand ( $r = -.10$ – $-.10$ ). No association with MC stability was found ( $r = -.01$ – $-.03$ ). AS were highly heritable (75%), while MC accuracy of the right hand and MC stability showed no genetic influences. For MC accuracy of the left hand, variance was explained by genetic (10%), common environmental (23%), and unique environmental variances. The association between MC accuracy of the left hand and AS was explained by a shared genetic influence but the genetic correlation was low ( $r = -.14$ ). The phenotypic and genetic associations between AS and computerized MC were weak, suggesting that fine MC is not a proper endophenotype for ADHD.

**Keywords:** ADHD; Genetics; Attention deficit; Twin study; Motor flexibility; Child.

## INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder in children, affecting approximately 5% of all school-aged children

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(Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). ADHD is characterized by inattentive, impulsive, and hyperactive symptoms that are highly heritable; 70% to 95% of the variation in ADHD symptoms (AS) is explained by genetic factors (Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2004; Thapar, O'Donovan, & Owen, 2005). About 30% to 50% of children with ADHD experience motor control (MC) problems (Fliers et al., 2008; Kadesjo & Gillberg, 1998) and it has been argued that the association between AS and MC might relate to a common genetic basis (Gillberg, 2003).

Kalff et al. (2003) indeed showed that fine MC problems are already observable in preschool children with an actual or putative diagnosis of ADHD. Fine MC was measured with a computerized Pursuit task (de Sonnevile, 1999) in 5-year-old children. The study demonstrated that children at risk for ADHD performed least accurate and least stable, followed by children later diagnosed with borderline ADHD. Healthy children and children with other psychopathologies performed most accurate and most stable.

The familial association between fine MC and AS was investigated by Slaats-Willemse, de Sonnevile, Swaab-Barneveld, and Buitelaar (2005) in a sample of ADHD children, their unaffected siblings, and healthy controls (mean age ~12 years old). MC was assessed with the same computerized Pursuit task. Children with ADHD and their unaffected siblings performed less accurate and less stable than control children, encouraging the authors to suggest that fine MC deficits may be associated with a genetic susceptibility for ADHD. In a more recent study, Rommelse et al. (2007) used the same experimental design as Slaats-Willemse et al. in a larger clinical sample of 12-year-old children. MC of children with ADHD was less accurate and less stable compared to healthy controls but this was only the case for MC of the left hand. Moreover, unaffected siblings performed similar to healthy controls. They did report, though, that unaffected siblings performed similar to the ADHD children (and worse than controls) with the left hand on a different computerized MC task (i.e., Tracking), suggesting again a familial basis for fine MC and ADHD. Recently, the shared etiology of ADHD and MC problems was examined in a clinical sib pair sample, which consisted of ADHD concordant and discordant sibling pairs, and healthy controls (Fliers et al., 2009). In this study, AS and MC were both rated with questionnaires. Also this study concluded that ADHD and MC, particularly fine motor problems, have a common familial basis.

Based on the previous results, it was suggested that MC might be a potential endophenotype for ADHD. An endophenotype is a measurable trait along the pathway between a disease and the distal genotype that may facilitate genetic analyses since they are more proximal to the pathology that underlies the disease phenotype (Gottesman & Gould, 2003). Endophenotypes must meet certain criteria; they must be heritable themselves and there should be a genetic association with the disorder of interest. The putative common genetic basis of AS and MC has been examined by one study so far (Martin, Piek, & Hay, 2006). In this study, participants were 5- to 16-year-old Australian twins ( $N = 1255$  pairs). AS were rated with the Australian Twin Behavior Rating Scale (ATBRs) and the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior scale (SWAN). MC was assessed with the Developmental Coordination Disorder Questionnaire (DCDQ). The heritability of MC was 69% in this sample, and the percentage of covariance between AS and MC attributable to genetic variance varied between 29% and 51%.

To sum up, both clinical and general population studies report an association between MC and AS. Sibling studies indicate a shared familial influence for both traits that is likely genetically determined as ADHD variance is for 75% explained by genetic factors. In the present study we investigated the genetic association between AS and fine

MC, using the computerized pursuit task as used in previous studies, in a population sample of twins and their siblings. With the powerful twin design, we aim to disentangle familial influences, into genetic and nongenetic (i.e., shared environmental) effects and to find additional support for the usefulness of fine MC as endophenotype for ADHD.

## METHODS

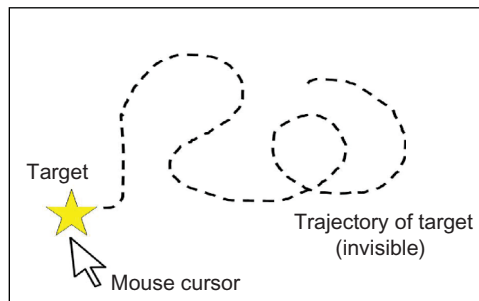
### Participants and Procedure

The sample consisted of a normal population of 354 twins, born between 1990 and 1992, and 55 of their siblings, born between 1986 and 1995. The twins were 12 years old (mean age = 12.42,  $SD = 0.16$ ), 27 siblings were younger than the twins (mean age = 9.60,  $SD = 0.71$ ), and 28 siblings were older (mean age = 14.69,  $SD = 0.60$ ). All twins were voluntarily registered at birth with the Netherlands Twin Registry (NTR) by their parents (Bartels et al., 2007). The participants participated in a longitudinal study on attention and cognition for which they performed a neuropsychological test battery at the VU University. Selection of twins took place when they were 5 years old and was based on age, sex, and zygosity. Of the original sample 75% participated again at age 12. There were no significant differences between responders and nonresponders for AS as reported by mothers and teachers at age 5 (Polderman, Gosso, et al., 2006). There were 41 monozygotic male twin pairs (MZM), 28 dizygotic male twin pairs (DZM), 56 monozygotic female twin pairs (MZF), 25 dizygotic female twin pairs (DZF), and 27 dizygotic opposite-sex twin pairs (DOS). In the same sex twin pairs, zygosity was determined on the basis of DNA polymorphisms. The study was approved by the institutional review board of the VU University, and parents and children signed an informed consent form prior to the assessment. None of the children suffered from severe physical or mental handicaps.

### Measures

**ADHD symptoms (AS).** Maternal ratings of AS were obtained with the Strengths and Weaknesses of ADHD and Normal behavior scale (SWAN; Swanson et al., 2009) during the neuropsychological assessment at the VU University. The SWAN consists of 18 items, based on the 18 ADHD items listed in the *Diagnostic and Statistical Manual of Mental Disorders* – fourth edition (*DSM-IV*). Items are rated on a 7-point scale ranging from “far below average” (1) to “far above average” (7), to allow for ratings of relative strengths and weaknesses. Item scores were summed to obtain an overall score. Low scores on this measure reflect relatively poor attention skills and a high expression of symptoms of hyperactivity/impulsivity, and high scores correspond to relatively good attention skills and relatively low expression of hyperactive/impulsive symptoms. In a general population, SWAN scores are normally distributed (Hay, Bennett, Levy, Sergeant, & Swanson, 2006; Polderman, Derks, et al., 2007).

**Motor control (MC).** MC was measured with a computerized pursuit task (see Figure 1). It is part of the Amsterdam Neuropsychological Tasks (ANT), of which the validity and reliability have been confirmed (de Sonneville, 1999). The task requires the child to follow an asterisk that moves across the computer screen (at a constant speed of 10 mm/s) in random directions, as closely as possible with the mouse cursor. The task



**Figure 1** Pursuit task. An asterisk moves in random directions across the computer screen and must be traced with the mouse cursor for 60 seconds with each hand. For the analyses, left-hand accuracy (mean distance between mouse cursor and target during the 60 s task) was used as measure of MC.

must be performed for 60 seconds, first with the preferred hand and then with the nonpreferred hand. Prior to the real test, participants could practice the task.

The mean distance in mm between the moving target and the mouse cursor was computed every second. The overall performance during 60 seconds was evaluated by computing the total mean distance of 60 deviation scores in mm (accuracy) and the standard deviation of the distances (stability).

The focus in this study will be on right- and left-hand data to make our results comparable with previous studies on fine MC and to link our results to left and right hemispheric regions in the brain.

**Covariates.** Based on previously reported effects of age, sex, hand preference, and birth weight on both AS and MC problems, these variables were included as covariates in the analyses (Kauranen & Vanharanta, 1996; Mick, Biederman, Prince, Fischer, & Faraone, 2002; Niederhofer, 2005; Whitaker et al., 2006). Birth weight was obtained from parental report. Hand preference was obtained from self-report. To this end, the child was allowed to choose “I am: 1) right-handed, 2) left-handed, or 3) ambidextrous” (i.e., using both hands with equal ease).

## Analyses

**Twin method.** The variation in a trait can be decomposed into sources of additive genetic variance (A), common environmental variance (C), and unique environmental variance (E). A is due to additive genetic effects of different alleles, C is due to environmental influences shared by family members, and E is due to environmental influences not shared by family members. Variance components can be estimated by statistical analysis of data from groups of individuals with different genetic relations but who share the same common environment, such as monozygotic (MZ) and dizygotic (DZ) twins and their singleton siblings. MZ twins (almost) always share 100% of their genes, while DZ twins and siblings share on average 50% of their segregating genes. To estimate genetic and nongenetic variance components, within pair resemblance of MZ twins is compared to within pair resemblance of DZ twins and siblings. If MZ within twin pair resemblance (i.e., the MZ correlation) for a certain trait is higher than DZ within twin pair resemblance (i.e., DZ correlation), and the resemblance between normal siblings (i.e., twin-sib correlation), the

presence of additive genetic variance is suggested. When DZ (and twin-sibling) correlations are lower than half the MZ correlation, genetic dominance may play a role.

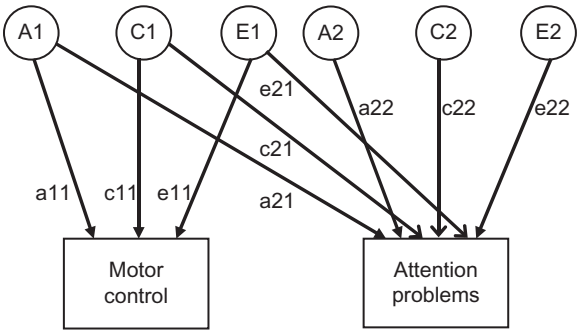
Twin analyses can be generalized to multivariate data, where the variation and covariation of multiple traits is decomposed into genetic and environmental sources. In this design, “cross trait-cross twin correlations” give an indication of how well a measure of trait A (for example MC) in one twin predicts a measure of trait B (for example AS) in the co-twin. The pattern of cross trait-cross twin correlations for MZ twins, DZ twins, and siblings indicates the relative contributions of genes and environment on covariance between traits (Boomsma, Busjahn, & Peltonen, 2002).

**Estimation procedures.** Analyses were performed using structural equation modelling in Mx (Neale, Boker, Xie, & Maes, 2006). Mx provides parameter estimates by maximizing the raw data likelihood, which involves that all data can be included in the analyses, also when certain data for participants are missing. Model fit is evaluated by hierarchic likelihood ratio ( $X^2$ ) tests. Specifically, the  $X^2$  statistic is computed by taking twice the difference between the log-likelihood (LL) of the full model and the log-likelihood of a reduced model,  $X^2 = -2(LL_0 - LL_1)$ . The associated degrees of freedom are computed as the difference in degrees of freedom between the two hierarchic models (Rijsdijk, 2007). A  $p$  value  $> .05$  indicates a relatively good fit of the tested model. In addition to the  $X^2$  statistic, Akaike’s Information Criterion (AIC) is computed,  $AIC = X^2 - (2 \cdot df)$ , which corrects for the number of parameters to be estimated (Akaike, 1987). A relatively low AIC value corresponds to a good fit.

**Descriptives.** Descriptive estimates, such as means, variances, phenotypic correlations, and twin correlations were obtained with Mx in a saturated model. This is a model that is fully parameterized and in which the covariance structure among relatives is allowed to take any value and is not modelled as a function of genetic and environmental factors. Correlations were estimated in  $6 \times 6$  correlation matrices (i.e., two traits for each twin and two traits for the sibling). Correlations were between traits, between twins per trait, between twins and siblings per trait, cross traits between twins (e.g., the correlation between MC of twin 1 and AS of twin 2), and cross traits between twins and siblings. To investigate the association between MC and AS, first we examined the phenotypic correlations between MC and AS. It was tested whether phenotypic correlations were equal for first born twins, second born twins and siblings, and equal for MZ and DZ twins. Secondly, we inspected the MZ and DZ twin correlations and twin-sibling correlations to examine the contribution of genetic and environmental influences on variation in MC and AS.

In subsequent analyses, it was tested whether means and variances were equal for firstborn and second-born MZ and DZ twins and siblings, whether cross twin-cross trait correlations were equal in first born and second born twins, and whether DZ cross trait-cross twin correlations were equal to cross trait-cross twin-sibling correlations. Effects of the covariates on the means of AS and MC were included in the saturated model as fixed effects. It was tested whether the effect of each covariate was equal in MZ, DZ twins, and siblings and if these effects were significant.

**Genetic analyses.** A decomposition of the  $6 \times 6$  phenotypic matrix into genetic (A) and environmental (C, E) covariance matrices was considered by means of a bivariate model with two observations; MC and AS (see Figure 2). First, a full ACE model that included the constraints and covariates as tested in the saturated model was fitted to the



**Figure 2** Bivariate model of motor control and attention problems for one individual:

$$\text{Heritability (h}^2\text{) motor control} = \frac{a_{11}^2}{a_{11}^2 + c_{11}^2 + e_{11}^2};$$

$$\text{Heritability (h}^2\text{) attention problems} = \frac{a_{21}^2 + a_{22}^2}{a_{21}^2 + a_{22}^2 + c_{21}^2 + c_{22}^2 + e_{21}^2 + e_{22}^2};$$

$$\text{Genetic correlation (r}_g\text{)} = \frac{a_{11} \times a_{21}}{\sqrt{a_{11}^2} \times \sqrt{a_{21}^2 + a_{22}^2}}.$$

data. Subsequently, AE and CE models were compared to the full ACE model to obtain the most parsimonious genetic model. E includes measurement error and is therefore always included in the models. The estimated genetic variance/covariance matrix can be standardized to obtain a genetic correlation between variables. It provides a measure of the extent to which traits are influenced by common genes. As the power to detect sex differences in variance components was low with the current sample size (Polderman, Posthuma, et al., 2006; Polderman, Stins, et al., 2006), male and female data were combined for both zygositys. However, there is no evidence for sex differences in heritability for AS (Derks, Hudziak, & Boomsma, 2009). Sex differences in the genetic architecture of MC have not been investigated yet.

## RESULTS

### Descriptives

Table 1 reports numbers, means, standard deviations, phenotypic correlations, and twin correlations of AS and MC. The SWAN was successfully completed for 339 twins and for 53 siblings. Due to technical problems, MC data were missing for eight twins and for two siblings. Participants with three *SDs* below or above mean scores of the MC task were excluded from the analyses as these scores likely reflect (a certain amount of) measurement error. Data on age, sex (47.2 % boys), and hand preference (86.4% right-handed) was known for all participants. Two children were ambidextrous and coded as missing. Birth weight ( $M = 2648.75$  g,  $SD = 595.14$ ) was present for all twins and for 48 siblings. Children with missing data on covariates were excluded from the analyses.

Phenotypic correlations were equal in MZ twins, DZ twins, and siblings. MC accuracy (for the left and for the right hand) and AS correlated  $-.10$  showing that lower scores

**Table 1** Numbers, Means, Standard Deviations, and Phenotypic Correlations of Motor Control (MC) and Attention Problems (AP).

	MC Accuracy Left Hand	MC Accuracy Right Hand	MC Stability Left Hand	MC Stability Right Hand	AP
<i>n</i> subjects	386	394	394	391	375
<i>n</i> complete MZ pairs	92	94	91	91	88
<i>n</i> complete DZ pairs	74	73	75	73	74
<i>n</i> siblings	44	52	52	52	44
Mean	3.95	2.57	3.59	2.37	78.34
Standard deviation	1.08	0.57	1.64	0.91	13.52
Phenotypic correlation with AP	-.10	-.10	-.03	.00	
MZ twin correlation	.35	.41	.19	.23	.86
DZ/twin-sibling correlation	.27	.54	.08	.39	.48

on the AS measure were weakly associated with higher mean deviation scores on the pursuit task (i.e., more AS were associated with lower MC). There was no association with MC stability ( $r = -.03/.00$ ). To check for possible nonlinear effects in the data we divided the sample, based on their AS scores, in three equal groups (low-middle-high). For these analyses the Mixed Modeling option in SPSS (15.0) was used, in which a correction for family dependency is applied (Beem & Boomsma, 2006). MC was the dependent variable, SWAN classification (i.e., low, middle, high), and the covariates were included as fixed effects, and family and zygosity status were incorporated as random effects. Parameter estimation was by maximum likelihood. The results showed no significant differences between groups except for accuracy of the right hand. For this measure a linear effect was found, with the lowest accuracy for participants with the most AS and the highest accuracy for participants with the least AS.

Twin-sibling correlations were equal to DZ twin correlations. The twin correlation patterns showed that an indication for additive genetic variance was present for MC accuracy of the left hand with the MZ correlation (.35) being slightly higher than the DZ/twin-sib correlation (.27). For MC accuracy of the right hand and MC stability, the twin correlations gave no indication for genetic variance. The twin correlations of AS clearly suggested the presence of genetic variance ( $r_{\text{MZ}} = .86$  and  $r_{\text{DZ/twin-sib}} = .48$ ).

To summarize, we found a weak phenotypic association between AS and MC accuracy but no association between AS and MC stability. Twin correlations indicated that genetic variance might play a role in MC accuracy of the left hand and clearly plays a role in AS. Therefore, in the subsequent genetic analyses the association between MC accuracy of the left hand and AS was further examined.

The variances of AS were equal among MZ and DZ firstborn and second-born twins and siblings. The variance of MC accuracy of the left hand was lower in second-born twins compared to firstborn twins and siblings. This variance difference was modelled in the genetic analyses by using a scalar effect, assuming that the components of genetic and environmental variance were proportioned to those observed in their siblings. Means of AS and MC accuracy of the left hand were equal in first- and second-born MZ and DZ twins and siblings and modelled as such in the genetic analyses.

The effect of each covariate on each variable could be equalized for MZ and DZ twins and siblings. Age had a positive effect on MC (one-year increase:  $-0.39$  mm,  $p < .001$ ) and affected the AS score positively (one-year increase:  $+1.98$  points,  $p = .06$ ).



Sex had only an effect on AS, with boys having more problems ( $-3.64$  points,  $p = .052$ ). Hand preference had a positive effect on MC (left-handed:  $-0.80$ ,  $p < .001$ ) and showed a trend for an effect on AS (left-handed:  $-1.42$  points,  $p = .12$ ). The effect of birth weight was significant for both variables (100 grams adding 0.51 points on the AS score, and  $-0.02$  mm on MC score, both  $p < .001$ ). Thus, most covariates showed (a trend for) a significant effect. Therefore all covariates, except the effect of sex on MC, were included in the genetic analyses.

### Genetic modelling

Cross twin-cross trait correlations of AS and MC accuracy of the left hand were equal in firstborn and second-born twins, and twin-sibling cross trait correlations were equal to DZ cross twin-cross trait correlations. Cross trait-cross twin correlations were low and with the current sample size not significantly different. Nevertheless, correlations were slightly higher in MZ twins compared to DZ twins ( $r_{MZ} = -.09$ ,  $r_{DZ} = -.06$ ; not in table) and this pattern may indicate that the phenotypic correlation is genetically mediated.

A bivariate analysis was conducted to examine heritability estimates of MC and AS and to investigate the sources of covariance between them (see Figure 2). Table 2 shows the fit statistics of these analyses. The ACE model showed for MC a small contribution of genetic (10%) and common environmental variance (23%) and a large contribution of unique environmental variance (67%). For AS, most of the variation was explained by genetic variance (75%). Reduced models, in which either the genetic variance (A) or the common environmental variance (C) was dropped, were compared to the full ACE model. A could not be dropped without significantly reducing the fit,  $X^2 = 41.70$ ,  $df = 3$ ,  $p < .001$ , indicating a significant genetic contribution on the variance and covariance of MC and AS. It was allowed to drop C from the model,  $X^2 = 2.37$ ,  $df = 3$ ,  $p = .50$ , and this increased the heritability of MC to 38% and of AS to 86%. However, the pattern of twin correlations indicated that the acceptable fit of this reduced model was probably due to the high heritability of AS and not of MC specifically.

**Table 2** Model Fitting Results of a Bivariate Model of Motor Control (MC) Accuracy of the Left Hand and ADHD Symptoms (AS).

Model	-2 times LL	$X^2$	$df$	$p$	AIC	Parameter Estimates					
						$a^2$		$c^2$		$e^2$	
						MC	AS	MC	AS	MC	AS
Saturated model	3880.19										
ACE model	3883.07	2.88 <sup>1</sup>	4	.58	-5.12	10	75	23	10	67	14
CE model	3924.77	41.70 <sup>2</sup>	3	<.001	35.70						
AE model	3885.44	2.37 <sup>2</sup>	3	.50	-3.63	38	86	-	-	62	14
drop $a^{21}$	3887.24	1.80 <sup>3</sup>	1	.18	-0.20						
drop $e^{21}$	3885.51	0.07 <sup>3</sup>	1	.79	-1.93						

*Note.* Saturated model represents the most parsimonious saturated model.

<sup>1</sup>The full ACE model is compared to the most parsimonious saturated model.

<sup>2</sup>The AE and CE model are compared to the ACE model.

<sup>3</sup>The models without genetic covariance or without unique environmental covariance are compared to the AE model.

Finally, we tested which variance component determined the association between MC and AS. To this end, we compared the fit of the AE model with only genetic covariance (i.e., without  $e^{21}$ ) to the AE model with only unique environmental covariance (i.e., without  $a^{21}$ ). The data were best described by the model that included genetic covariance,  $X^2 = 0.07$ ,  $df = 1$ ,  $p = .79$ ), compared to the model including unique environmental covariance,  $X^2 = 1.80$ ,  $df = 1$ ,  $p = .07$ . This indicated that the correlation of MC and AS can best be explained by shared genes. However, the genetic correlation between MC and AS was low ( $r = -.14$ ).

## DISCUSSION

This is the first study investigating fine motor control (MC), assessed with a computerized pursuit task, and ADHD symptoms (AS) in a twin design. The phenotypic correlations demonstrated that AS were only weakly associated with MC; the highest correlation was  $-.10$  for left and right hand accuracy. This was a lower correlation than expected according to the results of Slaats-Willemse et al. (2005) and Rommelse et al. (2007). They found linear effects between AS and fine MC when comparing participants with ADHD, their unaffected siblings, and controls. We performed similar analyses in the current data set by dividing the participants in low-, middle-, and high-scoring groups of AS. Now, we did find a significant effect for right hand but not for left hand accuracy, but the pattern of differences was linear and gave no explanation for the low correlation. Possibly, the difference in population (i.e., clinical samples versus the current normal population sample) explains the dissimilar results. However, regarding the Pursuit task, as used in the current study and in the previous studies by Slaats-Willemse et al. (2005) and Rommelse et al. (2007), the evidence for MC problems was not fully convincing. Slaats-Willemse et al. found that nonaffected siblings of ADHD families performed similar to their affected siblings and significantly worse than controls. However, limitations of the Slaats-Willemse et al. study were the small sample size (25 cases, 25 nonaffected siblings, and 48 controls) and no report on left- or right-hand performance. Rommelse et al. reported for the Pursuit task differences between cases and controls, but only for the left hand. A genetic relation was not supported as there were no performance differences between non-affected siblings and controls. More compelling seems the relation between questionnaire-reported MC (i.e., the Developmental Coordination Disorder Questionnaire [DCDQ], including a fine MC scale) and ADHD as an (genetic) association was reported in a clinical sample (Fliers et al. 2009) and normal population twin sample (Martin et al. 2006).

Although the heritability of AS is well established, the heritability of MC has been subject in only one previous study (Martin et al., 2006). Twin correlation patterns of MC measures showed for left-hand accuracy an indication for genetic influences, but not for the other MC measures. The heritability estimate of left-hand accuracy was 10%, while 23% of the variation was explained by common environmental variance, and 67% by unique environmental variance. By fitting a reduced model without common environmental variance, the heritability increased to 38%. This estimate is still much lower than the estimate of 64% as reported by Martin et al. (2006) in a sample of approximately same-aged children. A likely explanation is the difference in instruments. We used a computerized pursuit task while Martin et al. assessed fine MC with the DCDQ. This questionnaire is filled out by parents and reports on fine MC of children in daily life.

Most of the variance of left-hand accuracy was explained by unique environmental variance that also includes measurement error. This could possibly explain the largest part

of this variance component. There are several reasons to assume that this was not the case. First, several previous studies used left-hand accuracy of the same task where it provided an accurate differentiation between cases and controls in studies in ADHD (Kalff et al., 2003; Rommelse et al., 2007; Slaats-Willemse et al., 2005) and phenylketonuria (PKU; Huijbregts et al., 2003). Second, for a subset of the sample ( $n = 20$ ) test-retest data were available. Participants were retested at home, approximately 6 months after the first assessment (for details see Polderman, Posthuma, et al., 2007). For left-hand accuracy the test-retest correlation was .71. Hence, measurement error might play a marginal role but does certainly not explain all 67% that was found in this study.

What kind of unique environmental influences could possibly play a role in MC of the left hand? One might think of certain brain processes that are involved in left-hand MC, particularly which are likely located in right hemispheric regions. It has been argued that the right hemisphere is specialized for coordinating and adapting motor functions in response to unexpected events (Dien, 2008). Since the pursuit task requires participants to focus on a target for 60 seconds and involves hand movements that require continuous adaptation to the unpredictable trajectory of the target, it can be suggested that performance on this task depends particularly on right hemispheric processing. A severe illness or trauma to the head could possibly explain disturbed right hemispheric functioning in a child. However, it is also possible that biological disturbances occurred very early in life (pre-, peri-, or postnatal).

For AS, the heritability estimate was 86%, confirming previously reported estimates of genetic influences on AS (Thapar et al., 2005). In spite of the fact that variation in AS is mostly explained by genetic variance, it has been hard to find the responsible genes so far. Recent meta-analyses on candidate gene studies (Gizer, Ficks, & Waldman, 2009) and genome-wide association studies in ADHD (Franke, Neale, & Faraone, 2009) show disappointing results. It is believed that ADHD is caused by many different genes, each with a small effect. The detection of these effects is difficult and large samples are needed (Flint & Munafò, 2006). For this reason a lot of effort has been put into the identification of reliable, quantitative, and robust endophenotypes that may elucidate the genetic pathways of ADHD. MC has been put forward as a potential endophenotype by Rommelse et al. (2007), Slaats-Willemse et al. (2005), and recently Fliers et al. (2009). Still, twin studies are needed to explicitly test two crucial features of endophenotypes, namely the heritability and the genetic correlation with the phenotype of interest. Indeed, the current twin study showed that the covariance of AS and fine MC of the left hand could be explained by genetic variance, indicating that they are associated as a result of a common genetic basis. The genetic correlation was low, and because the heritability of MC accuracy of the left hand was also low, the current results do not support the view that fine MC of the left hand is a useful endophenotype. Additionally, twin correlations of fine MC of the right hand and of stability of the left and right hand gave no indication for genetic influences. For that reason, clinicians, but also gene finding studies, aiming to benefit from more distinct phenotypes of ADHD should focus on alternative endophenotypes. This could be for example IQ (Kuntsi et al., 2004; Polderman et al., 2009) or inhibitory control (Nigg, 2001; Willcutt et al., 2005); although for the latter, conflicting results have been reported as well (Polderman et al., 2009; van Mourik, Oosterlaan, Sergeant, 2005).

The results in this study should be considered in the context of some important limitations. First, only a small and specific component of MC was examined and therefore our results may not apply to other MC measures. However, previous studies on fine MC used the same Pursuit task that enabled us to properly compare results. Second, the sample size

was limited, particularly to estimate dominant genetic effects. The twin correlations however did not indicate that these kinds of genetic effects played a role.

In conclusion, this study showed that genetic variance plays no important role in stability or accuracy of fine MC of the left and right hand. In addition, only accuracy of the left hand showed a genetic association with ADHD symptoms, but this correlation was low. Thus, the current results do not suggest that fine MC, as measured with a computerized pursuit task, might be a proper endophenotype for ADHD.

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